IMMULITE® 2000 Anti-CCP IgG Assay

APR 0 4 2013

510(k) Summary as Required by 21 CFR 807.92

A. 510(k) Number	K121576
B. Purpose for Submission	New device
C. Measurand	Anti-cyclic citrullinated peptide (CCP) antibodies
D. Type of test	Semi-quantitative chemiluminescent immunometric assay
E. Applicant:	Siemens Healthcare Diagnostics Inc. 511 Benedict Avenue Tarrytown, NY 10591
F. Proprietary and Established Names:	IMMULITE®2000 Anti-CCP IgG Assay
G. Regulatory Information:	
1. Regulation section:	21 CFR 866.5775
2. Classification:	Class II
3. Products Codes:	NHX - Antibodies, Anti-Cyclic Citrullinated Peptide (CCP) JIT- Calibrators JJX – Single Analyte Control
4. Panel:	Immunology (82)
H. Intended Use:	The IMMULITE 2000 Anti-CCP IgG assay is an *in vitro* diagnostic immunoassay for the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum (including Serum Separator Tubes) or plasma (EDTA or lithium heparin) on the IMMULITE® 2000 system. Detection of anti-CCP antibodies is used as an aid in the diagnosis of Rheumatoid Arthritis (RA) and should be used in conjunction with other clinical information. Autoantibody levels represent one parameter in a multi-criteria diagnostic process, encompassing both clinical and laboratory-based assessments.

I. Device Description:

The IMMULITE 2000 Anti-CCP IgG assay consists of the following components:

- Anti-CCP IgG bead pack coated with cyclic citrullinated peptide (CCP) antigen
- Anti-CCP IgG reagent wedge containing bovine calf intestine conjugated to a monoclonal murine anti-human IgG antibody
- Anti-CCP IgG adjustors, low and high, containing lyophilized human serum with IgG reactive to CCP
- Anti-CCP IgG controls, negative and positive, containing human serum
- Autoantibody sample diluent containing protein/buffer matrix

J. Substantial Equivalence Information:

Predicate device name: DIASTAT™ Anti-Cyclic Citrullinated Peptide (anti-CCP) ELISA

510(k) number: k023285

Comparison with predicate:

A comparison of the device features, intended use, laboratory data and other information demonstrates that the IMMULITE ® 2000 Anti-CCP IgG assay is substantially equivalent to the predicate device, DIASTAT™ Anti-Cyclic Citrullinated Peptide (anti-CCP) ELISA, as summarized in the following tables.

SIMILARITIES		
Item	**Device**	**Predicate**
	IMMULITE 2000 Anti-CCP IgG Assay	**DIASTAT™ Anti-Cyclic Citrullinated Peptide (anti-CCP) ELISA**
Intended Use	The IMMULITE® 2000 Anti-CCP IgG assay is an *in vitro* diagnostic immunoassay for the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma on the IMMULITE®2000 system. Detection of anti-CCP antibodies is used as an aid in the diagnosis of Rheumatoid Arthritis (RA) and should be used in conjunction with other clinical information. Autoantibody levels represent one parameter in a multi-criteria diagnostic process, encompassing both clinical and laboratory-based assessments.	The DIASTAT™ Anti-CCP test is a semi-quantitative/qualitative enzyme-linked immunosorbent assay (ELISA) for the detection of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum or plasma. The test is intended to aid in the diagnosis of Rheumatoid Arthritis (RA) and is not definitive in isolation. Autoantibody levels represent one parameter in a multi-criterion diagnostic process, encompassing both clinical and laboratory-based assessments.
Antigen Used on the Solid Phase	Synthetic cyclic citrullinated peptide, second generation	Same
Detecting Antibody	Murine monoclonal antibody conjugated to Alkaline Phosphatase	Same
Controls	Negative and positive kit controls	Same
Interference	Rheumatoid factor (up to 200 IU/mL does not interfere with anti-CCP antibody results.	Same

DIFFERENCES		
Item	**Device**	**Predicate**
	IMMULITE® 2000 **Anti-CCP IgG Assay**	**DIASTAT™ Anti-Cyclic Citrullinated Peptide (anti-CCP) ELISA**
Assay format	Solid-phase, two-cycle sequential chemiluminescent immunometric assay	Enzyme-linked immunosorbent assay (ELISA)
Substrate	Chemiluminescent	Mg2+, phenolphthalein monophosphate (PMP)
Sample size	5 µL (20 µL of the prediluted sample)	10 µL (100 µL of the prediluted sample)
Sample Dilution	1:40	1:100
Sample Types	Serum or plasma (EDTA, lithium heparin)	Serum or plasma (EDTA, lithium heparin, sodium citrate)
Incubation	30 minutes, 30 minutes, 5 minutes	60 minutes, 30 minutes, 30 minutes
LoD	1.50 U/mL	0.05 U/mL
Expected Values (apparently healthy donors)	Median: <1.50 U/mL Range: <1.50 U/mL	Mean : 0.63 ± 0.419U/mL Range: 0.05 - 3.8U/mL
Reportable Range	1.50 - 200 U/mL	0.05 – 100U/mL
Assay Cut-off	≥4.00 U/mL = Reactive	>5 U/mL = Positive
Interference	Bilirubin (up to 0.2 mg/L), hemoglobin (up to 500 mg/dL), and triglycerides (up to 1.5 g/dL) do not interfere with anti-CCP antibody results. Total protein not assessed.	Bilirubin (up to 0.2 mg/mL), hemoglobin (up to 400 mg/dL), and intralipid (up to 15 mg/mL) do not interfere with anti-CCP antibody results. Total Protein up to 120 mg/mL does not interfere with anti-CCP antibody results.

K. Standard/Guidance Documents Referenced:

CLSI EP5-A2 Evaluation of Precision Performance of Quantitative Measurement Methods
CLSI EP6-A Evaluation of the Linearity of Quantitative Measurement
CLSI EP17-A Protocols for Determination of Limits of Detection and Limits of Quantitation
CEN 13640 Stability Testing of In Vitro Diagnostic Reagents

L. Test Principle:

The IMMULITE® 2000 Anti-CCP IgG assay is a solid phase, two-cycle sequential chemiluminescent immunometric assay. In the first cycle, the patient sample and the buffer are incubated together with the coated bead for 30 minutes. During this time, human IgG in the sample binds to CCP on the bead. Unbound sample is then removed by centrifugal washes. In the second cycle, the enzyme conjugated monoclonal murine antihuman IgG is added to the original reaction tube for additional 30 minutes incubation. The enzyme conjugated monoclonal murine anti-human IgG antibody binds to immobilized anti-CCP IgG on the bead. The unbound enzyme conjugate is removed by centrifugal washes. Finally, chemiluminescent substrate is added to the reaction tube containing the bead and the signal is generated in proportion to the bound enzyme.

M. Performance Characteristics

1. Analytical Performance:
   a. *Precision/Reproducibility:*
   Precision was evaluated using a protocol based on CLSI document EP05-A2, Evaluation of Precision Performance of Quantitative Measurement Methods. Eleven samples were tested over a period of 20 days, using 2 IMMULITE® 2000 instruments with 2 reagent lots each, 2 runs per day and 2 replicates per sample. The work list consisted of a high control and 2 sets of six-member precision panels: one serum donor panel and one lithium heparin plasma donor panel. Precision panels were prepared by pooling the samples and spiking to the desired concentration with a stock Anti-CCP reactive sample. The sample concentrations are detailed in the table below:

Sample	Target Concentration (U/mL)
LPIC2.101 Positive control	46.0
SERP2 serum donor panel	2.96
SERP3 serum donor panel	4.8
SERP4 serum donor panel	9.0
SERP5 serum donor panel	37.4
SERP6 serum donor panel	135.5
PLASP2 Li Heparin donor panel	2.59
PLASP3 Li Heparin donor panel	4.9
PLASP4 Li Heparin donor panel	9.0
PLASP5 Li Heparin donor panel	37.4

Sample	Target Concentration (U/mL)
PLASP6 Li Heparin donor panel	135.5

Precision data is summarized in the table below:

20-Day Imprecision N=320		Between Lot		Between Day		Between Run		Within Run		Total	
Sample	Mean U/mL	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LPIC2	47.4	0.18	0.4	0.00	0.0	0.90	1.9	1.84	3.9	2.05	4.3
SERP2	2.1	0.20	9.3	0.15	6.9	0.15	6.8	0.20	9.4	0.29	13.6
SERP3	4.3	0.08	1.8	0.13	3.1	0.17	3.9	0.28	6.5	0.35	8.2
SERP4	8.5	0.00	0.0	0.18	2.1	0.24	2.9	0.34	4.0	0.46	5.4
SERP5	37.6	0.66	1.8	0.96	2.6	1.12	3.0	1.54	4.1	2.13	5.7
SERP6	144.0	2.29	1.6	1.25	0.9	4.17	2.9	5.45	3.8	6.98	4.8
PLASP2	2.4	0.16	6.7	0.17	6.8	0.17	7.1	0.20	8.2	0.31	12.8
PLASP3	4.5	0.18	3.8	0.17	3.6	0.20	4.5	0.29	6.4	0.39	8.6
PLASP4	8.4	0.00	0.0	0.05	0.6	0.31	3.7	0.35	4.1	0.47	5.6
PLASP5	38.5	0.11	0.3	0.54	1.4	1.04	2.7	1.57	4.0	1.96	5.0
PLASP6	141.5	1.06	0.7	2.23	1.6	3.87	2.7	5.52	3.9	7.11	5.0

Reproducibility was evaluated using two different reagent lots at three external testing sites, using serum donor panels from the precision study. The protocol was run over 10 days, 2 runs per day, with 4 replicates per run for the sample pools and control material.

The results for reproducibility, pooled across 3 sites, are presented in the table below.

Sample ID	N	Mean (U/mL)	Within Run		Between Run		Between Day		Between Site		Total Within-Device		Total Within-Lot	
			SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)
Reagent Lot 201														
SERP2	244	1.94	0.20	10.1	0.06	3.2	0.11	6.0	0.17	8.7	0.23	12.0	0.29	14.8
SERP3	244	3.98	0.22	5.6	0.12	2.9	0.11	3.0	0.14	3.6	0.27	6.9	0.31	7.8
SERP4	244	8.08	0.37	4.5	0.07	0.8	0.17	2.0	0.18	2.3	0.41	5.1	0.45	5.6
SERP5	243	36.07	1.48	4.1	0.50	1.4	0.61	2.0	0.84	2.3	1.68	4.6	1.88	5.2
SERP6	244	139.18	5.11	3.7	2.84	2.0	1.25	1.0	3.79	2.7	5.98	4.3	7.08	5.1

Sample ID	N	Mean	Within Run		Between Run		Between Day		Between Site		Total Within-Device		Total Within-Lot	
		(U/mL)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)	SD Index	CV (%)
LPIC2	246	45.66	1.97	4.3	0.56	1.2	0.83	2.0	1.55	3.4	2.21	4.8	2.70	5.9
Reagent Lot 202														
SERP2	228	1.61	0.19	11.7	0.04	2.2	0.13	8.0	0.16	10	0.23	14.4	0.28	17.6
SERP3	240	3.72	0.25	6.7	0.09	2.4	0.21	6.0	0.15	4.1	0.34	9.1	0.37	10
SERP4	240	8.02	0.41	5.2	0.22	2.7	0.16	2.0	0.27	3.4	0.50	6.2	0.56	7.0
SERP5	240	36.79	1.36	3.7	0.86	2.3	0.89	2.0	1.10	3.0	1.84	5.0	2.14	5.8
SERP6	240	139.61	6.27	4.5	2.46	1.8	4.81	3.0	4.81	3.4	8.28	5.9	9.58	6.9
LPIC2	240	43.54	2.49	5.7	0	0	1.61	4.0	1.65	3.8	2.97	6.8	3.39	7.8

b. *Linearity/assay Reportable Range:* The Anti-CCP Linearity study was performed according to the CLSI document EP6-A; Evaluation of the Linearity of Quantitative Measurement Methods. A dilution series was prepared by combining a reactive serum pool and a non-reactive serum pool in different ratios to produce 11 dilutions covering the assay measuring range (1.50 U/mL to 200 U/mL). The dilutions were run in triplicate on one IMMULITE®2000 instrument. Results are shown below. Since this assay has no reference material or method and is traceable to internal standard, the recovery is defined as the difference between the observed dose and the fitted values of the linear equation.

Dose Recovery:

Sample	Expected Dose (U/mL)	Mean Observed Dose (U/mL)	Linear Fitted Dose (U/mL)	Mean % Recovery
P3	181.51	182.93	183.00	100.0%
P4	151.38	158.52	152.70	103.8%
P5	121.26	127.68	122.40	104.3%
P6	91.13	93.00	92.09	101.0%
P7	61.00	61.91	61.79	100.2%
P8	30.87	28.32	31.49	89.9%
P9	15.80	17.01	16.34	104.1%
P10	12.07	11.89	12.58	94.5%
P11	8.33	8.58	8.82	97.3%
P12	4.43	4.48	4.89	91.5%
P13	2.64	2.40	3.10	77.4%

c. *Traceability, Stability, Expected Values (controls, calibrators, methods):*

Traceability - There is no recognized standard reference material for Anti-CCP. The IMMULITE® 2000 Anti-CCP IgG assay is traceable to an internal standard and manufactured using qualified materials and measurement procedures.

Stability - Freshly opened and prepared IMMULITE® 2000 Anti-CCP IgG adjustors and controls showed 30 days open vial stability when stored at 2-8°C, or 6 months (aliquotted) when stored at -20°C. The IMMULITE® 2000 Anti-CCP IgG reagent wedge is stable at 2-8°C until the expiration date on the label.

Adjustors and Controls are prepared in house and arbitrary units are assigned during the development process. Calibrator and Control values are summarized in the tables below. The listed values are approximate values, as the values are lot specific.

Adjustor	Dose Range U/mL
Low	2.0 – 5.0
High	40 - 60

Control	Target* U/mL
Low	<1.5
High	44

d. *Detection Limit:*

Limit of Blank (LoB): An Anti-CCP nonreactive donor sample was used as a blank and was analyzed on three IMMULITE® 2000 instruments over 5 days. The sample was tested twice daily using two lots of reagent with two replicate per run. The LoB result was determined by applying a nonparametric principle based on ranked ordered value using the following equation:

$LoB = [N_B(p/100)+0.5]$; where $p=(100-\alpha) = 95$ and NB = number of blank measurements = 732

The LoB was the average of the ranked results at positions 695 and 696. The LoB was determined to be 0.26 U/mL.

Limit of Detection (LoD): Five Anti-CCP serum samples (mean concentrations ranging from 0.26 to 2.5 U/mL) were assayed in replicates of 6 using 2 reagent kit lots run for 5 days with 2 runs per day. Two instrument and 2 operators generated 960 observations.

LoD = LoB +median -5th percentile.

LoD = 0.26 + 1.4 -0.2 = 1.46 U/mL.

e. *Analytical Specificity:*

Endogenous Interferents: A study was conducted to assess the effect of several endogenous interferents on the IMMULITE®2000 Anti-CCP IgG assay. Testing consisted of the addition of human serum albumin, triglycerides, hemoglobin, bilirubin (conjugated and unconjugated), and rheumatoid factor into the samples. One control sample and five (5) different sample pools with differing Anti-CCP concentrations (range 2.0 U/mL to 205 U/mL) were used. Each potentially interfering substance was spiked separately into the sample pools. Results are shown in the table below.

IMMULITE 2000 Anti-CCP: Summary of Endogenous Interferents in Anti-CCP Samples	% Difference: Control Dose / Test Dose: Lot 201	% Difference: Control Dose / Test Dose: Lot 202	Mean % Interference Lot 201 & Lot 202
Human Serum Albumin (12 g/dL)	1.2	6.9	4.1
Triglycerides (1.5 g/dL)	1.8	-1.4	0.2
Hemoglobin (500 mg/dL)	4.5	2.1	3.3
Conjugated Bilirubin (0.2 mg/mL)	-1.6	-2.0	-1.8
Unconjugated Bilirubin (0.2 mg/mL)	-3.6	-2.9	-3.3
Rheumatoid Factor (200 IU/mL)	0.8	-4.1	-1.7

Less than 10% mean interference was found with all endogenous interfering substance as follows: Human Serum Albumin (up to 12g/dL); Triglycerides (up to 1.5 g/dl); Hemoglobin (500 mg/dL); Bilirubin: Conjugated and Unconjugated (up to 0.2 mg/mL each); and Rheumatoid Factor (up to 200 IU/mL). However, individual samples occasionally showed > ± 10% interference.

Hook Effect: Not applicable. The IMMULITE® 2000 Anti-CCP assay is a 2-cycle assay with sample containing anti-CCP antibodies first binding to the CCP peptide immobilized on the polystyrene capture bead. Excess unbound antibody is removed by washing prior to the second cycle reagent incubation. During the second cycle, an anti-human IgG alkaline phosphatase conjugate binds in turn to the anti-CCP antibody bound to the bead.

Assay response is positively related to the amount of anti-CCP antibody bound to the capture bead up to the point where the CCP determinants are saturated with antibody, at which point the response plateaus. Any unbound anti-CCP beyond the reportable range of the assay and in excess of saturation is removed by washing prior to contact with the reagent conjugate and there is no risk that a hook effect will be observed.

f. *Assay cut-off:*

A high Anti-CCP IgG positive defibrinated plasma unit was arbitrarily assigned with a value of 1000 U/mL. A lot of reference calibrators was prepared by diluting the positive unit with negative normal human serum. The reference calibrators were value-assigned by the dilution factor in relationship to the neat values of 1000 U/mL.

A total of 388 samples consisting of 212 apparently healthy samples, 106 RA positive samples, 70 anti-CCP positive samples, as determined by a 3rd party method, were tested with IMMULITE 2000 Anti-CCP Kit and the DIASTAT Anti-CCP ELISA.

The cutoff of the IMMULITE® 2000 Anti-CCP IgG assay was determined with positive and negative patient samples by a ROC analysis, with a balanced consideration of sensitivity and specificity. A result greater than or equal to 4U/mL indicates that anti-CCP IgG antibodies were detected in the sample. A result of less than 4U/mL indicates that anti-CCP IgG antibodies were not detected in the sample.

2. Comparison Studies

a. *Method Comparison with predicate device:*

Method Comparison: The IMMULITE® 2000 Anti-CCP IgG assay was compared to the predicate Axis-Shield DIASTAT™ Anti-CCP assay using two lots of reagents. Each sample was tested in singlicate using 3 IMMULITE® 2000 instruments. For reagent lot 1, 255 unaltered patient serum samples were tested, 229 of which were determined to be reactive and 26 nonreactive using the DIASTAT™ assay. For reagent lot 2, 256 unaltered patient serum samples were tested, 230 of which were determined to be reactive and 26 nonreactive using the DIASTAT™ assay. Results are shown in the tables below.

Reagent lot 1:

	IMMULITE 2000 Anti-CCP IgG			
DIASTAT	Reactive	Non-Reactive	Percent Positive Agreement	Percent Negative Agreement
Positive	199	30	86.9%	46.2%
Negative	14	12		

Total Agreement: 82.2%

Reagent lot 2:

IMMULITE 2000 Anti-CCP IgG

DIASTAT	Reactive	Non-Reactive	Percent Positive Agreement	Percent Negative Agreement
Positive	198	32	86.1%	42.3%
Negative	15	11		

Total Agreement: 81.6%

b. *Matrix Comparison:*

Thirty-nine matched serum and plasma samples were collected in the following anti-coagulant tubes: serum clot tube, Lithium Heparin plasma tube, serum separator tube (SST), and EDTA plasma tube. Twenty-one of the 39 samples were spiked to achieve Anti-CCP levels across the assay measuring range. Data was analyzed using Deming regression plots.

SERUM vs.	Correlation Coefficient	Slope	Intercept	Means
Lithium Heparin	1.000	1.020	-0.46	52.9 U/mL
SST Serum	1.000	1.020	-0.52	53.0 U/mL
EDTA Plasma	1.000	1.010	-0.31	52.2 U/mL
				Serum: 52.3 U/mL

3. Clinical Studies:
   a. *Clinical Sensitivity and Specificity*

Clinical Performance Study: The assay was performed on the IMMULITE® 2000 to assess the clinical sensitivity and specificity of well-characterized samples.

A total of 1512 patient serum samples were collected for the study. 1048 samples were rheumatoid arthritis (RA) positive and the remaining 464 samples were from non-RA patients with potentially cross-reactive diseases. RA positive patients were classified according to the ACR criteria.

IMMULITE 2000 Anti-CCP IgG

Clinical Status	Reactive	Non-Reactive	Sensitivity	Specificity
Positive	667	381	63.6%	97.0%
Negative	14	450		

b. *Other clinical supportive data (when a. and b. are not applicable):*
Not applicable.

4. Clinical Cut-off:
Same as assay cut-off.

5. Expected Values/Reference Range:
A total of 200 serum samples from presumed healthy male and female donors were analyzed using the IMMULITE® 2000 Anti-CCP IgG assay. The results from this study suggest a median of <1.5 U/mL, and a 99th percentile of 4.06 U/mL. Expected values in the normal population should be negative. Each laboratory should establish a reference range appropriate to their patient populations and clinical practice.

IMMULITE® 2000 Anti-CCP IgG CVM

510(k) Summary as Required by 21 CFR 807.92

A. 510(k) Number	
B. Purpose for Submission	New device
C. Measurand	Anti-cyclic citrullinated peptide (CCP) antibodies
D. Type of test	Calibration verification material for IMMULITE Anti-CCP IgG assay
E. Applicant:	Siemens Healthcare Diagnostics Inc. 511 Benedict Avenue Tarrytown, NY 10591
F. Proprietary and Established Name:	IMMULITE® 2000 Anti-CCP IgG Calibration Verification Material
G. Regulatory Information:	
1. Regulation section:	21 CFR 862.1660
2. Classification:	Class I (reserved)
3. Products Codes:	JJX – Single Analyte Control (assayed and unassayed)
4. Panel:	Clinical Chemistry (75)
H. Intended Use:	The IMMULITE 2000 Anti-CCP IgG Calibration Verification Material is for *in vitro* diagnostic use, as a control for calibration verification of the IMMULITE® 2000 Anti-CCP IgG assay on the IMMULITE 2000 system.
I. Device Description:	The IMMULITE Anti-CCP IgG Calibration Verification Material consists of one set of four vials, containing low, intermediate and high levels of lyophilized human serum with IgG reactive to cyclic citrullinated peptide (CCP), in buffer with preservative, plus an anti-CCP-free sample. Source materials derived from human blood were tested and found nonreactive for syphilis; for antibodies to HIV 1 and 2; for hepatitis B surface antigen; and for antibodies to hepatitis C.
J. Substantial Equivalence Information:	**Predicate device name**: Elecsys Anti-CCP CalCheck **510(k) number**: K091601

Comparison with predicate:
A comparison of the device features, intended use, and other information demonstrates that the IMMULITE ® 2000 Anti-CCP IgG Calibration Verification Material is substantially equivalent to the predicate device, Roche Elecsys Anti-CCP CalCheck, as summarized in the following tables.

SIMILARITIES		
Item	**Device**	**Predicate**
	IMMULITE Anti-CCP IgG CVM	**Elecsys Anti-CCP CalCheck**
Intended Use	For *in vitro* diagnostic use, as a control for calibration verification of Anti-CCP IgG assay.	Same
Format	Lyophilized	Same
Matrix	Human serum	Same
Handling	Reconstitute with distilled or deionized water	Same

DIFFERENCES		
Item	**Device**	**Predicate**
	IMMULITE Anti-CCP IgG CVM	**Elecsys Anti-CCP CalCheck**
Analyzer	For use on IMMULITE 2000 analyzer	For use on Elecsys 2010, MODULAR ANALYTICS E170, cobas e411 and cobas e601 analyzers
CVM Levels	4	3

K. Standard/Guidance Documents Referenced:

- Guidance for Industry and FDA Staff – Assayed and Unassayed Quality Control Material

L. Test Principle:

- Not Applicable

M. Performance Characteristics

6. Analytical Performance:
   a. *Precision/Reproducibility:* Not Applicable
   b. *Linearity/assay reportable range:* Not Applicable
   c. *Traceability, Stability, Expected values:*

Traceability - Since there is no recognized standard reference material for Anti-CCP, the IMMULITE 2000 Anti-CCP IgG assay is traceable to an internal standard and manufactured using qualified materials and measurement procedures. The IMMULITE Anti-CCP Calibration Verification Material (CVM) is traceable to this standard.

Stability - Open vial stability – Freshly opened and reconstituted IMMULITE 2000 Anti-CCP CVMs showed 30 days open vial stability when stored at 2-8°C. Unopened stability is indicated by expiration date on the label when stored at 2-8°C.

Value Assignment: The Anti-CCP reference calibrator values were assigned by using an approved internal standard. This reference standard lot is used to assign Anti-CCP IgG CVMs. Quality control is then performed by calculating the recovery of controls using the reference calibration verification material.

Each CVM level below was run in duplicate on 3 different reagent kit lots (Lot 201, 202 and 211) and 14-15 runs per lot for a total of 86 replicates. Five instruments were used to carry out all the runs. The analyte values were calculated based on the recovered values for each run independently. The average analyte recovered for each CVM level determined the value assigned to the Target Mean.

The Guideline Range (95% confidence interval) for each CVM level was established based on the Target Mean and ± 2 Standard Deviations (SD).

Level	Catalog and Lot number	Target Mean (U/mL)*	SD	Guideline Range (U/mL)		Total CV%	Spec CV%
1	L2PICVM1 Dxxx	0.00		≤ 1.50		NA**	NA
2	L2PICVM2 Dxxx	6.19	0.41	5.37	7.00	6.6%	10%
3	L2PICVM3 Dxxx	103	8.85	85.3	121	8.6%	10%
4	L2PICVM4 Dxxx	209	21.09	167	252	10%	10%

* note that CVM value assignment is lot-specific
** NA = Not Applicable

d. *Detection limit:* Not Applicable
e. *Analytical Specificity:* Not Applicable
f. *Assay cut-off:* Not Applicable

7. Comparison Studies
   a. *Method Comparison with predicate device:* Not Applicable
   b. *Matrix Comparison:* Not Applicable

8. Clinical Studies:
   a. *Clinical Sensitivity and Specificity:* Not Applicable
   b. *Other clinical supportive data (when a. and b. are not applicable):* Not Applicable

9. Clinical Cut-off: Not Applicable

10. Expected Values/Reference Range:
    See Value Assignment above.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

April 4, 2013

Siemens Healthcare Diagnostics
c/o Susan Brocchi
Sr. Regulatory Affairs Specialist
511 Benedict Avenue
Tarrytown, NY 10591

Re: k121576
Trade/Device Name: IMMULITE 2000 Anti-CCP IgG Assay and IMMULITE 2000 Anti-CCP IgG Calibration Verification Material
Regulation Number: 21 §CFR 866.5775
Regulation Name: Rheumatoid factor immunological test system
Regulatory Class: Class II
Product Code: NHX, JIT
Dated: March 29, 2013
Received: April 1, 2013

Dear Ms. Brocchi:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21

CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Maria M. Chan -S

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics and Radiological Health (OIR)
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): k121576

Device Name: IMMULITE® 2000 Anti-CCP IgG Assay and Calibration Verification Material

Indications for Use: The IMMULITE 2000 Anti-CCP IgG assay is an *in vitro* diagnostic immunoassay for the semi-quantitative determination of the IgG class of autoantibodies specific to cyclic citrullinated peptide (CCP) in human serum (including Serum Separator Tubes) or plasma (EDTA or lithium heparin) on the IMMULITE 2000 system. Detection of anti-CCP antibodies is used as an aid in the diagnosis of Rheumatoid Arthritis (RA) and should be used in conjunction with other clinical information. Autoantibody levels represent one parameter in a multi-criteria diagnostic process, encompassing both clinical and laboratory-based assessments.

The IMMULITE 2000 Anti-CCP IgG Calibration Verification Material (CVM) is for *in vitro* diagnostic use, as a control for calibration verification of the IMMULITE 2000 Anti-CCP IgG assay on the IMMULITE 2000 system.

Prescription Use X And/Or Over the Counter Use_____

(21 CFR Part 801 Subpart D) (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostics and Radiological Health (OIR)

Maria M. Chan -S

Division Sign-Off
Office of In Vitro Diagnostics and Radiological Health

510(k) k121576